Subst'd 1 cont'd

44. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the neutral lipid is DOPE.

45. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the lipid portion further comprises a PEG-lipid.

Subst'd

46. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the lipid portion further comprises cholesterol.

REMARKS

The Invention

The present invention is directed to methods of treating a neoplasia in a mammal involving administering to the mammal a serum stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion. Administration of the nucleic acid-lipid particle is by injection at a site distal to the neoplasia in the mammal. In some embodiments, the lipid portion of the nucleic acid-lipid particle comprises a cationic lipid and a neutral lipid. In some embodiments, a prodrug is also administered to the mammal. In other embodiments, a chemotherapeutic agent is also administered to the mammal.

Status of the Claims

Applicants wish to thank Examiner Zara for extending the courtesy of the telephonic interview held on June 20, 2002 with Applicants' representatives Carol Fang and Eugenia Garrett-Wackowski. During this interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. Applicants thank Examiner Zara for her time.

After entry of this amendment, claims 1-46 are pending. Claims 1-28 stand rejected under 35 U.S.C. §112, first paragraph. This rejection is addressed below.

New claims 35-46 have been added. Support for new claims 35-46 is found throughout the specification and claims as originally filed. Thus, no new matter is added by these amendments.

Applicants request that new claims 35-46 in the present Amendment be entered under 37 C.F.R. § 1.114.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner initially maintained the rejection of claims 1-28 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement.

As previously explained, a particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).

> As MPEP § 2164.02 states, "[a] rigorous or an invariable exact correlation is not required" between a particular model and a specific condition.
>
> As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

During the interview, Applicants discussed several aspects of the rejection with the Examiner. For example, it was pointed out to the Examiner that the specification provides (1) teachings regarding therapeutic nucleic acids; (2) teachings regarding preparation and properties of lipid-nucleic acid particles; (3) teachings regarding neoplasias suitable for treatment using the lipid-nucleic acid particles of the present invention; and (4) teachings regarding administration of lipid-nucleic acid particles (*see, e.g.*, page 10, line 14 to page 14, line 24; page 14, line 25 to page 18, line 31; page 19, line 28, to page 20, line 16; and page 21, lines 20 to page 22, lines 27). Moreover, as discussed with the Examiner, the teachings in the specification are affirmed by the Declaration of Dr. Ian MacLachlan, submitted on March 8, 2002 in response to the Final Office Action mailed October 10, 2001. For the convenience of the Examiner, a copy of the declaration is attached as Appendix C.

The Examiner previously acknowledged that the claims are enabled for treatment effects comprising the administration of the nucleic acid encoding HSV-TK and ganciclovir, which nucleic acid is fully encapsulated in the lipid formulations explicitly disclosed (*see,* Office Action pages 2-3), but alleged that undue experimentation is required to enable treatment of any neoplasia in an animal (*see,* Advisory Action). As discussed during the interview, Applicants have demonstrated that distal administration of the nucleic acid-lipid particles of the claimed invention can be used to treat multiple types of neoplasia with multiple classes of nucleic acids (Declaration ¶8 and ¶12).

For example, the specification and declaration of Dr. MacLachlan contain multiple working examples demonstrating effective *in vivo* treatment of diverse

neoplasias such as melanoma, sarcoma, fibrosarcoma, and colorectal tumors with multiple classes of nucleic acids encapsulated in the lipid-nucleic acid particles of the claimed invention. During the interview, the additional experimental results presented in the Dr. MacLachlan's declaration and the working examples in the specification were discussed in detail. Specifically, the additional experiments show that diverse classes of nucleic acids encoding cytokines (*e.g.*, IL-12), tumor suppressor proteins (*e.g.*, apoptin), and bacterial toxins (*e.g.*, *Pseudomonas* exotoxin) encapsulated in the lipid-nucleic acid particles of the invention effectively inhibit growth of diverse neoplasias such as sarcoma and colon carcinoma (*see,* Declaration ¶7, ¶8, and ¶12, and Exhibits B, C, and D). Applicants also pointed out the working examples in the specification which showed that growth of melanoma, fibrosarcoma, and colorectal tumors was inhibited by distal administration of nucleic acids encoding the suicide gene HSV-TK encapsulated in the lipid-nucleic acid particles of the present invention (*see,* Declaration ¶8). The Examiner agreed that all of these data were persuasive in supporting the scope of the claims. The Examiner also agreed that Dr. MacLachlan's declaration at ¶6 affirms that administration of serum stable lipid-nucleic acid particles of the present invention by injection at a site ***distal*** to a neoplasia in a mammal is effective for treating neoplasias.

Applicants also noted that further *in vitro* experiments demonstrating that multiple suicide enzymes (purine nucleoside phosphorylase and cytosine deaminase) are effective in inhibiting tumor cell proliferation (*see*, Declaration ¶12). The Examiner agreed that there was inhibition of tumor cell growth, but thought that the *in vivo* results discussed above were more persuasive in supporting the breadth of the claims.

The Examiner also raised the issue of the lipid composition of the lipid-nucleic acid particle. As explained during the interview, the lipid formulation typically comprises a cationic lipid (*e.g.*, DODAC), a neutral lipid (*e.g.*, DOPE), and optionally comprises a PEG-lipid (*e.g.*, PEG-ceramide) or an ATTA-lipid. These formulations and their preparation are fully supported by the specification at, *e.g.*, page 14, line 25 to page 18, line 31 and Example 1 (page 23, lines 15-24). *See also,* Declaration ¶10. As

suggested by the Examiner, Applicants have added new claims 42-46 which specifically recite the lipid composition of the lipid-nucleic acid particles of the present invention.

In continuing discussion, Applicants noted for the Examiner that in their formulations the nucleic acids are fully encapsulated within the lipid-nucleic acid particles of the present invention. As explained by the Applicants, other lipid-nucleic acid particles in the art are lipoplexes of lipid and nucleic acid, *i.e.*, complexes of lipids with nucleic acids in which the nucleic acids are ***not*** encapsulated. Since the nucleic acids of the lipid-nucleic acid particles of the present invention are fully encapsulated, degradation of the nucleic acids by nucleases is greatly reduced.

The Examiner had previously asserted that prevention of degradation by nucleases does not prove the efficacy of the methods. As explained in the declaration of Dr. MacLachlan, the specification sets forth three sets of experiments showing that nucleic acids administered in the lipid-nucleic acid particles of the present invention ***are*** expressed *in vivo*. In each experiment, mice were first injected with neoplastic cells. 10, 14, or 11 and 17 days later, mice were injected with lipid-nucleic acid particles containing nucleic acids encoding reporter genes (*e.g.*, luciferase) or HSV-TK (*see*, Declaration ¶7). Mice were sacrificed at various time points after injection of the lipid-nucleic acid particles and assayed for expression of the luciferase or HSV-TK. In each case, expression of the luciferase or HSV-TK was ***actuall***y detected, thus demonstrating that nucleic acids administered in the lipid-nucleic acid particles of the present invention are expressed.

Finally, Applicants would like to note that Dr. MacLachlan explains that the references cited by the Examiner in the Office Action of April 10, 2001 as allegedly illustrating the state of the art with regard to gene therapy ***support*** the proposition that lipid-nucleic acid particles can effectively be used to deliver therapeutic nucleic acids to neoplasias, *i.e.*, that treatment of neoplasias using lipid-nucleic acid particles is effective (*see,* Declaration ¶13).

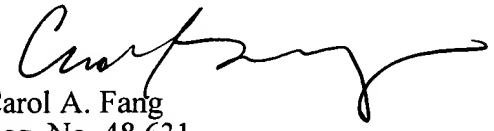
Therefore, a skilled artisan, using the teachings of the specification either alone or together with what is known to those of skill in the art, would be able to practice the invention as claimed, ***without*** undue experimentation.

In view of the foregoing remarks, Applicants assert that claims 1-28 are fully enabled by the specification as originally filed. Accordingly, Applicants respectfully request that the rejection under § 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



Carol A. Fang
Reg. No. 48,631

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
CAF:pja
SF 1353028 v1

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

35. (New) A method of treating a neoplasia in a mammal, in accordance with claim 5, wherein said gene encodes a suicide enzyme.

36. (New) A method of treating neoplasia in a mammal in accordance with claim 35, further comprising administering a prodrug.

37. (New) A method of treating a neoplasia in a mammal in accordance with claim 36, wherein said prodrug is administered after the serum stable nucleic acid-lipid particle.

38. (New) A method of treating a neoplasia in a mammal in accordance with claim 36, wherein said prodrug is administered before the serum stable nucleic acid-lipid particle.

39. (New) A method of treating a neoplasia in a mammal in accordance with claim 9, further comprising administering a chemotherapeutic agent.

40. (New) A method of treating a neoplasia in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered after the serum stable nucleic acid-lipid particle.

41. (New) A method of treating a neoplasia in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered before the serum stable nucleic acid-lipid particle.

42. (New) A method of treating a neoplasia in a mammal in accordance with claim 1, wherein the lipid portion comprises a cationic lipid and a neutral lipid.

43. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the cationic lipid is DODAC.

44. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the neutral lipid is DOPE.

45. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the lipid portion further comprises a PEG-lipid.

46. (New) A method of treating a neoplasia in a mammal in accordance with claim 42, wherein the lipid portion further comprises cholesterol.